

# PSYCHOPHARMACOLOGY:

## Focus on Aripiprazole: A Review of its use in Child and Adolescent Psychiatry

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### ABSTRACT

**Objective:** To review published literature regarding aripiprazole in child and adolescent psychiatry. **Method:** A literature review was conducted using the MEDLINE search term: 'aripiprazole' with limits: Human trials, English language, All Child (aged 0-18 years). Additional articles were identified from reference information and poster presentation data. **Results:** Aripiprazole is an atypical antipsychotic which was recently approved for use in Canada, but has been available for several years in the United States. Pharmacologically, aripiprazole is a partial agonist at D<sub>2</sub> and 5-HT<sub>1A</sub> receptors and an antagonist at 5-HT<sub>2A</sub> receptors. Randomized controlled trial data is available showing efficacy for aripiprazole in the treatment of children and adolescents with schizophrenia, bipolar disorder and behavioural problems associated with autism. Open-label evidence is also available for use of aripiprazole in other disorders such as tic disorders, aggression and disruptive behavior disorders. Unlike some other available atypical antipsychotics, there does not appear to be any effect on QTc interval on the electrocardiogram. Adverse effects including extrapyramidal symptoms (EPS), akathisia, sedation, headache, nausea were significant in clinical trials in children and adolescents. The possibility of aripiprazole causing tardive dyskinesia cannot be excluded. In this population, aripiprazole appears to have minimal impact on the metabolic profile compared to most other atypical antipsychotics, with minimal changes in weight or body mass index, no significant changes in glucose or lipid metabolism, and a decrease in serum prolactin. **Conclusion:** Aripiprazole may represent an important alternative for some children and adolescents who have experienced poor efficacy or significant metabolic adverse effects with their current antipsychotic treatment regimen.

### RÉSUMÉ

**Objectif:** Examiner la documentation publiée sur l'aripiprazole en psychiatrie de l'enfant et de l'adolescent. **Méthode:** Un examen de la documentation a été effectué par le biais de la recherche terminologique sur MEDline pour les termes: aripiprazole et ses limites, essais sur les humains, langue anglaise, enfants (0-18 ans). Des articles supplémentaires ont été identifiés dans des documents de référence et des données de présentations de communications par affichage. **Résultats:** L'aripiprazole est un antipsychotique atypique dont l'emploi a récemment été approuvé au Canada mais qui est disponible aux États-Unis depuis plusieurs années. En matière de pharmacologie, l'aripiprazole est un agoniste partiel des récepteurs D<sub>2</sub> et 5-HT<sub>1A</sub> et un antagoniste des récepteurs 5-HT<sub>2A</sub>. Les données relatives aux essais contrôlés pris au hasard sont disponibles, elles indiquent l'efficacité de l'aripiprazole pour traiter les enfants et les adolescents qui souffrent de schizophrénie, de trouble bipolaire et de problèmes de comportement associés à l'autisme. L'évidence ouverte est également disponible pour l'emploi de l'aripiprazole pour traiter d'autres problèmes tels que les tics, l'agression et les désordres disruptifs de comportement. Contrairement à certains autres antipsychotiques atypiques disponibles, il ne semble pas y avoir d'effets sur l'intervalle QTc de l'électrocardiogramme. Les effets indésirables tels que les symptômes extra-pyramidaux, l'akathisie, la sédation, le chagrin, la nausée étaient significatifs lors des essais cliniques parmi les enfants et les adolescents. La possibilité que l'aripiprazole cause une dyskinésie tardive ne peut pas être exclue. Parmi cette population, l'aripiprazole semble avoir des effets minimes sur le profil métabolique, par rapport à la plupart des autres antipsychotiques atypiques: les changements de poids ou de l'indice de masse corporelle sont minimes, les changements de métabolisme du glucose ou des lipides sont insignifiants et la sécrétion de prolactine est en baisse. **Conclusion:** L'aripiprazole représente peut-être une alternative importante pour certains enfants et adolescents qui ont eu des résultats peu efficaces ou des effets métaboliques indésirables significatifs avec le traitement antipsychotique qu'ils suivent actuellement.

### Introduction

Aripiprazole (Abilify®, Bristol Myers Squibb) received a Notice of Compliance from Health Canada in July 2009, and will become available in Canada in early fall 2009. It was approved by the United States (US) Food and Drug

Administration (FDA) in 2002 and is the seventh atypical approved by Health Canada (in addition to clozapine, risperidone, olanzapine, quetiapine, paliperidone and most recently ziprasidone).

There is widespread use of this class of medications in pediatric age groups, including FDA approved indications for risperidone and aripiprazole (Ortho-McNeil-Janssen Pharmaceuticals, Inc., 2007; Otsuka Pharmaceutical Co., 2008). Aripiprazole is approved specifically for treatment of Bipolar I Disorder (in children aged 10-17 years) and Schizophrenia (in children aged

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13-17 years) by the FDA. None of the atypical antipsychotics have received approval from Health Canada for use in any indication for patients under the age of 18 years, and Bristol-Myers Squibb did not apply for any pediatric indications as part of their initial submission to Health Canada for aripiprazole. Due to the availability of aripiprazole in the US and other countries for several years prior to its launch in Canada, a significant amount of literature regarding use of aripiprazole in children and adolescents has been published. This review will focus on the available evidence and clinical experience regarding the use of aripiprazole in child and adolescent psychiatry.

### **Pharmacology**

Aripiprazole is sometimes referred to as a third-generation antipsychotic to denote a difference from other available atypical (second-generation) antipsychotics. Unlike other atypicals which have varying levels of D<sub>2</sub> receptor antagonism, aripiprazole is a partial agonist at dopamine D<sub>2</sub> and serotonin 5-HT<sub>1A</sub> receptors (Otsuka Pharmaceutical Co., 2008). This means that aripiprazole is able to modulate the degree of the blockade of these receptors. If the level of blockade at these receptors is very high, when aripiprazole is present, it will produce a net lowering of the strength of the blockade. If the level of blockade at the receptors is low, when aripiprazole is present, it will produce a net increase in the level of blockade. In common with other atypicals, aripiprazole is also an antagonist at 5-HT<sub>2A</sub> receptors. Aripiprazole also has strong affinity for D<sub>3</sub> receptors, moderate affinity for D<sub>4</sub>, 5-HT<sub>2C</sub>, 5-HT<sub>7</sub>, alpha-1 adrenergic receptors, histamine H<sub>1</sub> receptors and the serotonin reuptake transporter, with no appreciable affinity at the cholinergic muscarinic receptor.

In a pharmacokinetic study of 21 children and adolescents (Findling et al., 2004), oral maintenance dose aripiprazole revealed linear (dose-proportional) pharmacokinetics, and a time to maximum serum concentration (T<sub>max</sub>) of 2 hours. Aripiprazole has a long serum half-life (T<sub>1/2</sub>) and though it was not calculated in this pediatric study due to termination of blood sample collection after 24 hours, T<sub>1/2</sub> has previously been reported to be 75 hours for aripiprazole in adults (Otsuka Pharmaceutical Co., 2008). There is one active metabolite, dehydroaripiprazole, which has been reported to have a T<sub>1/2</sub> in adults of 94 hours. Though pharmacokinetic parameters were similar in children and adolescents compared to adults, for equivalent doses, children and adolescents had mean peak steady-state concentrations (C<sub>max</sub>) that were higher than observed in adults, with T<sub>max</sub> occurring more rapidly compared to adults. Based on these observations, children may be more susceptible to dose-related side

effects of aripiprazole treatment, and gradual upwards titration of aripiprazole to the target dose may help to minimize adverse effects in this population. Aripiprazole may be administered once daily, and its absorption does not appear to be affected by food. Aripiprazole is a major substrate of both cytochrome p450 (CYP) 2D6 and 3A4 enzymes, and may be subject to interactions with other drugs that are strong inhibitors or inducers of these enzymes. Aripiprazole does not have inhibitory or inducing effects on these or other CYP enzymes.

### **Efficacy Data**

A review of the literature was conducted using the MEDLINE search term: 'aripiprazole' with limits: Human trials, English language, All Child (aged 0-18 years). Additional articles were identified from reference information and poster presentation data. Table 1 summarizes the published pediatric literature on aripiprazole. The studies are ranked by Level of Evidence (Centre for Evidence Based Medicine, 2009).

There have been four prospective, randomized control trials (RCT) of aripiprazole in children or adolescents. In a multicenter trial (Findling et al., 2008a), 302 subjects with Schizophrenia, aged 13-17 years, were randomized to receive either aripiprazole 10 mg/day, aripiprazole 30 mg/day or placebo for six weeks. The primary outcome was the Positive and Negative Symptom Scale (PANSS) from baseline to endpoint. Secondary outcomes were measured using the Clinical Global Impression-Improvement and Severity (CGI-I, CGI-S) and the Children's Global Assessment Scale (CGAS). Aripiprazole was found to be superior to placebo in the treatment of adolescents with Schizophrenia. There was a significant reduction in the overall PANSS score in both the 10 and 30 mg/day groups compared to placebo.

The significant reductions were noticed by week one in the 30 mg/day group however by week six in this same group there was only significant reduction in the positive subscale and not in the negative subscale. In the 10 mg/day group both positive and negative subscales showed significant reductions but not until the trial endpoint at week six.

Owen (Owen et al., 2008a) enrolled 98 children and adolescents aged 6-17 years with serious behavioural problems associated with Autism in a flexible dose (aripiprazole 2-15 mg/day) 8 week trial.

The behavioural problems were identified as tantrums, aggression and self-injurious behaviour. Primary efficacy outcomes were measured by the caregiver-rated Aberrant Behaviour Checklist-Irritability (ABC-I). Secondary outcomes were measured by the CGI-I, CGI-S, the other ABC subscale scores and the Children's Yale-

**Table 1 - Review of aripiprazole evidence in children and adolescents**

Level of Evidence	Author/Journal	Year and Report Type	# of pts (n), % males	Indication(s)	Aripiprazole Daily Dose	Aripiprazole Monotherapy?	Duration of treatment	Adverse Effects		Metabolic effects
								Pooled reporting of flexible and fixed-dose trials (% above PI, * score denotes improvement)	Pooled reporting of flexible and fixed-dose trials (% below PI, -score denotes improvement)	
1b	Chey-Lisse P, APA poster presentations NF2-061, NR2-063 (flexible-dose trial)	2008; Owen R, AACAP poster presentation 3.59	n=98 (87% male)	Autistic Disorders	Flexible Dose (range: 2-15 mg) vs placebo	Yes (implied)	8 weeks	ABC-1, CSQ, PedsOL	ABC-4: (treatment difference vs PI, + score denotes improvement) -9 (-11%, tremor (10%), sedation (10%), vomiting (8%), somnolence (6%) decreased appetite (7%), increased salivation (5%))	Pooled reporting of flexible and fixed-dose trials: Mean BMI change PI: 0.2; A: 0.7 Mean BMI Z-score change: PI: 0.01/-0.11 Negligible changes in glucose, lipids
1b	Owen R, AACAP poster presentation	2008; Owen R, AACAP poster presentation 3.59	n=218 (89% male)	Autistic Disorders	5-10 or 15 mg vs placebo (randomization)	Yes (implied)	8 weeks	ABC-1, CSQ, PedsOL	ABC-4: (treatment difference vs PI, + score denotes improvement) -9 (-11%, tremor (10%), sedation (10%), vomiting (8%), somnolence (6%) decreased appetite (5%), increased salivation (5%))	Pooled reporting of flexible and fixed-dose trials: Mean BMI change PI: 0.2; A: 0.7 Mean BMI Z-score change: PI: 0.01/-0.11 Negligible changes in glucose, lipids

Ib	Prospective Randomized Controlled Trial	Corey-Lise P.; Karen L.; NBS presentations NBS-061, NBS-063 (fivedose trial)	n=21/18 (89% male)	Ph: 10.2 ± 3.1 A10 ± 2.8 A15 ± 3.1	Autistic Disorders vs placebo (1:1; randomization)	5, 10 or 15 mg Yes (implied) 8 weeks
2009;						Pooled reporting of flexible and fixed-dose trials: - score denotes improvement:
2008b;						Mean weight change: Pi: -0.4 kg, A10: 1.5 kg EPS: -0.1 kg, A10: 0.2 kg CSQ: -0.1 kg, A10: 0.2 kg SOM: -0.1 kg, A10: 0.2 kg MAD: -0.1 kg, A10: 0.2 kg HRSD: -0.1 kg, A10: 0.2 kg fever: +0.1 kg, A10: 0.2 kg sommolence: -0.6%, A10: 0.6% appetite: +5%, A10: 0.11 kg Negligible changes in glucose, lipids

<b>1b</b>	<b>Prospective Randomized Controlled Trial (1b)</b>	2008a; Finding RL; Am J Psychiatry	n=302 (57% males) (range: 13-17)	Schizophrenia	10 or 30 mg vs placebo (1:1 ratio)	Yes (adjuvant benzodiazepines or clonazepam permitted)	CGAs, CGI-I, OGLs, PANSS, CGS week 6 change; Pt: +9.8 ± 1.3; A10: +4.7 ± 1.5; A16: +4.4 ± 1.3; A24: +2.7 ± 1.4; A30: 2.5 ± 0.1; CGS week 6 changes; Pt: -0.9 ± 0.1; A10: -1.2 ± 0.1; A30: -1.3 ± 0.1	Side effects occurring at ≥ 5% incidence relative to placebo: Pt: 3.2 ± 3.4g A10: EPS 8%; headache 6%; A16: EPS 7%; somnolence 7%; A24: EPS 7%; somnolence 16%; A30: EPS 7%; somnolence 7%; tremor (10%), akathisia (7%)	Mean weight changes: Pt: 0.1 ± 2.6 Kg; A10: 0 ± 2.1 Kg; A30mg: 0.2 ± 2.3 Kg A16: 0.2 ± 2.5 Kg; A24: 0.1 ± 2.5 Kg; A30: 0.1 ± 2.5 Kg
<b>1b</b>	<b>Prospective Open label trial</b>	2009; Bastiens L; Community Mental Health J	n=468 (70% males)	11.9 ± 2.6 (range 6-7)	Agression (target group); Conduct Disorder; 30%)	Assigned to A or Z in nonrandomized fashion	CGI, GAF, HALFS, OAS, pMRS	OAS: 70% of A completers (58% by ITT) had ≥ 50% decrease in OAS. (A mean change 6.8 ± 1.8 to 2.3 ± 2.9); 71% of B completers (45% by ITT) had ≥ 50% decrease in OAS. (Z mean change 7.4 ± 2.2 to 3.1 ± 2); CGI: mean rating at endpoint: A: 2.1 ± 1.1; B: 1.7 ± 1.1; GAF: A: 50 ± 4.7 to 16.1 ± 7.7; HALFS: A: 4.4 ± 2.4 to 3.7 ± 3.9; OAS: 4.4 ± 2.4 to 1.6 ± 1.7; pMRS: A: 2.4 ± 1.6 to 1.3 ± 1.4; Z: 8.8 ± 4.7 to 11.6 ± 3.6	

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<sup>a</sup> Level of Evidence - as per Centre for Evidence Based Medicine document (2009)  
 Abbreviations BMI=Body Mass Index CPK=Creatine Phosphokinase EIPS=extrapyramidal symptoms HbA1c=c-glycosylated Hemoglobin A1c

Intention-to-treat analysis

- | <b>Abbreviations of Rating Scales used</b> |   |
|--|---|
| ABC-I                                      | Aberrant Behavior Checklist Irritability subscale                   |
| ABSI                                       | Adult ADHD Rating Scale-IV  |
| BAS-B                                      | Barkley Adult Inventory   |
| BAT  | Buckley Anxiety Inventory   |
| BPRS                                       | Brief Psychiatric Rating Scale                                      |
| CDSRS                                      | Children's Depression Rating Scale - Revised)                       |
| DDCS                                       | Childhood Depression Scale for Schoolchildren                       |
| DCS  | Childhood Global Assessment Scale                                   |
| DCR  | Diagnostic Classification Research                                  |
| DERS                                       | Dimensional Emotion Regulation Scale                                |
| EEG  | Electroencephalogram  |
| FCBIS                                      | Frontal Cognitive Impairment Scale                                  |
| GCI  | Global Clinical Impression  |
| GCSQ                                       | Caregiver Stress Questionnaire                                      |
| YACB-S                                     | Children's Yale-Brown Obsessive Compulsive Scale (modified for PDD) |
| GBI  | General Behavior Inventory  |
| HAFS                                       | Health and Life Functioning Scale                                   |
| HOMS                                       | Homies-Capricious Quality of Life Scale                             |
| MOVES                                      | Moto and Vocal I Evaluation Scale                                   |
| OAS  | Overt Aggression Scale  |
| PANS                                       | Positive and Negative Symptom Scale                                 |
| PEPSOL                                     | Pediatric Quality of Life Inventory                                 |
| PMSES                                      | Parent Multidimensional Stress Scale                                |
| SFSS                                       | Social Functioning Scale  |
| SPS  | Scale of Frontal Symptomatology                                     |
| VABS                                       | Vineland Adaptive Behavior Scales                                   |
| YCTBS                                      | Yale Global Severity Scale  |

FOCUS ON ARIPIPRAZOLE: A REVIEW OF ITS USE IN CHILD AND ADOLESCENT PSYCHIATRY

2b	Prospective Open label trial	2009; Slager K; JCAP	n=25 (76% males)	8.6 (range: 5-17)	PDD-NOS, Asperger's Disorder	7.8 mg (range: 2.5-15 mg)	Yes	14 weeks	<b>ABC, CG-I, CY-BOCS-PDD, VABS</b>	ABC: 29 ± 7.3 to 8.1 ± 7.5 CG-I: 88% rated as much improved or very much improved (CG-I ≤ 2) and with ≥ 25% improvement on ABC CY-BOCS-PDD: 11.9 ± 2 to 6.8 ± 1 VABS: improvement on socialization domain noted	tiredness (58%), cough (48%), increased appetite (44%), nausea/vomiting (40%), constipation (36%), dry mouth (32%), dyspepsia (32%), salivation (16%), tremor (12%) Mean BMI change: 20.3 ± 1.5 ± 5.7 Prolactin levels decreased significantly; no significant change in blood glucose or lipids noted
2b	Prospective Open label trial (2b)	2008; Felding R; J Clin Psychopharmacol	n=15 (67% male)	12.2 ± 3.7 (Range: 10-17)	Tourette Disorder or Chronic Tic Disorder	8.17 ± 4.68 mg (range: 2.5-15 mg)	Monotherapy in 60%	12 weeks	<b>CG-I, CG-I-S</b>	CG-I: 85% of all pts much improved or very much improved (CG-I ≤ 2) CG-I-S: A20: 3.7 ± 2.3; A25: 3.7 ± 1.2	headache (29%), abdominal pain (24%), dizziness (19%), vomiting (14%), fatigue (10%), stiffness (5%), dysuria (10%), somnolence (10%) No clinically relevant changes in prolactin, cholesterol or triglycerides
2b	Prospective Open label trial	2008; Felding R; J Clin Psychopharmacol	n=21 (61% male)	12.2 ± 2.1 (Range: 10-17)	Bipolar Disorder, Tourette Syndrome, schizophrenia, ADHD, OCD, PDD	Titrated to 20.5 or various ratio)	Yes (67% on concomitant non- psychotropic medications)	2 weeks (at target dose)	<b>CG-I, CG-I-S</b>	CG-I: 85% of all pts much improved or very much improved (CG-I ≤ 2) CG-I-S: A20: 3.7 ± 2.3; A25: 3.7 ± 1.2	headache (29%), abdominal pain (24%), dizziness (19%), vomiting (14%), fatigue (10%), stiffness (5%), dysuria (10%), somnolence (10%) No clinically relevant changes in prolactin, cholesterol or triglycerides
2b	Prospective Open label trial	2008; Felding R; J Clin Psychopharmacol	n=23 (61% male)	10.2 ± 1.4 (range: 8-12)	ADHD/Combined subtype or Inattentive subtype	6.7 ± 2.4 mg	35% pre-treated with stimulants were stopped on enrollment)	6 weeks	<b>ARS-N, CGAS, CG-I, CG-I-S</b>	ARS-N: 3.6 ± 1.5 to 2.15 ± 1.1 CGAS: 62.8 ± 4.1 to 71 ± 8.6 CG-I: 9% much improved or very much improved (CG-I ≤ 2) CG-I-S: 4 ± 3.2 ± 0.7	headache (75%), nausea (47%), abdominal pain (26%), no prior stimulant Rx: 1-7.7 kg (30% increased appetite (28%), EPS (22%), musculoskeletal pain (22%), hiccups (12%), fatigue (9%), dysuria (9%), 9% discontinued due to weight gain (13%), headache (7%), vomiting (3%), sore throat (13%)) Protein: 4.45 ± 1.45 to 3.88 ± 2.61 (p<0.05)
2b	Prospective Open label trial	2007; Yoo H; J Clin Psychiatry	n=24 (79% male)	11.8 ± 3.8	TIC Disorders	9.8 ± 4.8 mg		8 weeks	<b>CG-I, CG-I-S, YGSS</b>	CG-I: 38% rated as much improved or very much improved (CG-I ≤ 2 at endpoint) YGSS: 26.7 ± 5.5 to 12.6 ± 7.6	parkinsonism (48%), hypertension (38%), headache (27%), headach (25%), EPS (22%), asthenia (22%), decreased appetite (8%), each
2b	Prospective Open label trial	2007; Woods S; Br J Psychiatry	n=15 (53% male)	17.1 ± 5.5	Prodromal Schizophrenia	15.7 ± 5.9 mg	Yes (benzodiazepines and anticholinergics permitted)	8 weeks	<b>BAL, CGS, GAF, HC-RF, SF-S, SOPs, YMRS</b>	(scores shown as change from baseline) BAL: 15.1 ± 11.2 CGS: 3.3 ± 4.2 GAF: +9.2 ± 5.3 HC-RF: +3.2 ± 5.1 SOPs: -2.21 ± 1.2 (p<0.001) YMRS: -3.9 ± 3.6	sedation (75%), irritability (33%), somnolence (53%), headache (27%), sedation (20%), increased appetite (27%), somnolence, memory impaired, increased perception impaired, excessive sweating (13% each)
2b	Prospective Open label trial	2007; Tomlina S; CNS Spectr	n=10 (50% male)	9.3 ± 3.5 (range: 8-17)	Juvenile Bipolar Disorder with comorbid ADHD	11.7 ± 5.7 mg	No	6 weeks	<b>CG-I-S, SNAP-II, YMRS</b>	CG-I-S: 4.4 ± 1.5 to 0.4 ± 1.63 SNAP-II: 18.6 ± 4.7 to 14.7 ± 4.7 YMRS: 35.5 ± 11.8 to 20.6 ± 11.68	salivation (70%), sedation (50%), decreased appetite (60%), decreased sedation (60%), increased appetite (50%), symptoms (60%), increased appetite (50%), decreased appetite (50%), sweating (50%), tremor (50%), nervousness/jitteriness (50%), suicidal ideation (20%)
2b	Prospective Open label trial (2b)	2007; Biederman J; CNS Spectr	n=19 (58% male)	11.6 ± 3.6 (range: 6-17)	Bipolar Disorder (I and II)	9.4 ± 4.2 mg	Monotherapy in 89% (11% receiving stimulants)	8 weeks	<b>BPRS, CDRS, CG-I, YMRS</b>	BPRS: 38.9 ± 7.1 to 28.8 ± 5.9; CDRS: 38.6 ± 11.2 to 32.2 ± 7.4; CG-I: 6% much improved or very much improved (CG-I ≤ 2)	sedation (70%), sedation/tiredness (60%), decreased appetite (60%), increased appetite (50%), decreased appetite (50%), headache (50%), akathisia (15%), sleep disturbance (15%), depression, suicide attempt (15%), GI upset (42%), headache (32%), akathisia (15%), sleep disturbance (20%)
2b	Prospective Open label trial	2006; Yoo H; JCAP	n=14 (80% male)	11.93 ± 3.41 (range: 7-17)	Tourette Disorder	10.88 mg (range: 2.5-15 mg)	Yes	8 weeks	<b>CG-I-S, SNAP-II, YMRS</b>	CG-I-S: 4.4 ± 1.5 to 0.4 ± 1.63 SNAP-II: 18.6 ± 4.7 to 14.7 ± 4.7 YMRS: 35.5 ± 11.8 to 20.6 ± 11.68	Nausea/vomiting (14%), hypersomnia (7%), weight gain (7%)
2b	Prospective Open label trial	2004; Slager K; JCAP	n=5 (100% male)	12.2 ± 5.07 (range: 5-18)	PDD-NOS	12 ± 2.4 mg (range: 2.5-15 mg)	40%	8 weeks	<b>CG-I</b>	CG-I: 100% rated as much improved or very much improved (CG-I ≤ 2)	No significant changes in weight, prolactin or metabolic parameters at 8 weeks;
2b	Prospective Open label trial	2004; Felding R; CINP poster presentation	n=23 (% males not reported)	range: 6-17	Conduct Disorder	Based on weight (range: -1.0 to 10 mg, mg after significant weight loss or gain of first 4 weeks)	mean 12 weeks (range: 8-16 weeks)	2 weeks	<b>CG-I</b>	CG-I: 64% of children (≤ 12) and 48% of adolescents (≥ 13) rated as much improved or very much improved (CG-I ≤ 2)	Mean weight change: +3.7 kg (range: +1.6 to +5.9); Some pts previously treated with other second generation antipsychotics
2b	Naturalistic Evaluation	2008; Budman C; JCAP	n=37 (70% males)	13.4 ± 2.8 (range: 8-18)	Tourette Disorder (64% also met criterion for ADHD (range: 2.5-40 mg) for ED)	11.7 ± 7.2 mg (range: 2.5-40 mg)	24%	6-12 weeks	<b>CG-I-Rage, CG-I-Ties</b>	CG-I-Rage: (in completers) 4.98 ± 1.22 to 2.53 ± 1.13; CG-I-Ties: (in completer) 4.38 ± 0.81 to 2.69 ± 0.88	akathisia (10%), agitation (8%), mood upset (8%), EPS (3%), extreme sedation (1%), headache, dizziness, nausea (3%), also rated not quantified); 8/27 pts discontinued study (22%)
2b	Naturalistic Evaluation	2007; Gibson A; Int Clin Psychopharmacol	n=45 (28% males)	15.1 ± 1.5 (range: 11-18)	Any Axis I diagnosis West common: bipolar disorder/schizoaffective (bipolar type) Diagn: 78% met criteria for ED)	16.9 ± 7.9 mg	No	31.3 ± 19.6 days	<b>CG-I, CG-I-S</b>	CG-I: 87% rated as much improved or very much improved (CG-I ≤ 2)	Mean weight change (2245 lbs): Weight data available in only 15 of 37 pts; Mean weight change: -3.6 kg (range: -2 to +5 lbs); 67% gained weight; Mean BMI change (2245 lbs): Mean weight change: 8.2 ± 5.6 kg (7 of 12 who lost weight were previously treated with another antipsychotic)
2b	Naturalistic Evaluation	2004; Bachzman D; JCAP	n=30 (60% male)	13 ± 3 (range: 5-19)	Bipolar disorder/schizoaffective (bipolar type)	9 ± 4 mg (range: 5-15 mg)	30%	4.4 ± 2.7 months (range: 1-9 months)	<b>CG-I, CG-I-S, CGAS</b>	CG-I: 67% much improved or very much improved (CG-I ≤ 2 at endpoint) CGAS: Significant improvement (mean: 48 ± 11 to 63 ± 11); CG-I-S: Significant improvement (mean: 4.2 ± 0.8 to 2.6 ± 1)	Sedation (33%), akathisia (23%), GI upset (33%), blury vision, speech (33%), headache, dizziness, nausea (3%), also rated not quantified); 8/27 pts discontinued study (22%)
Case Series	Case Series	2008; Bachzman C.J.; Ther Drug Monit	n=33 (55% male)	18.7 ± 1.7 (range: 13.5-21.6)	Schizophrenia Spectrum Disorders	12.9 mg ± 6.4 mg (range: 5-36 mg)	No	range 14-489 days (naturalistic study)	Not reported	Not reported	



Case Report 2005; Wahl R, Am J Psychiatry	n=1 (female)	17	Schizophrenia	15 mg	No (continued on resumption of long- acting injection)	12 days	None	Not reported	
Case Report 2005; Neigh B; JAACAP	n=1 (male)	16	Bipolar Disorder NOS PDD-NOS	5 mg	No	Approximately 1 month. Pt also receiving lithium and ocarbazepine	None	Not reported	2 episodes of palpitations. Spontaneously resolved. Ocarbazepine discontinued. Palpitations did not recur.
Case Report 2005; Kantens V; JAACAP	n=1 (male)	17	Bipolar Disorder (Type I)	12.5 mg	No	6 months, then tapered off over 2 week period	None	Not reported	Abnormal movements of jaw, tongue and hands, facial twitches - Diagnosed as white muscle stiffness. Resolved after 3 weeks, following treatment with branched chain amino acids.
Case Report 2004; Myers W; JAACAP	n=1 (female)	17	Delusional Disorder, Erotomanic type	10 mg	Yes	5 months	None	Lessening of delusional beliefs beginning at week 2 and maximal at week 8	Not reported

Brown Obsessive-Compulsive Scale (CY-BOCS). Results showed significant improvement starting by week one in all the scales in the flexible dosing group over placebo.

Owen (Owen et al., 2008b) also enrolled 218 subjects, aged 6-17 years with behavioural problems associated with Autism in a fixed dose (aripiprazole 5, 10 or 15 mg/day or placebo) 8 week trial. The same outcome measures were used as in the flexible dose trial and significant improvements were observed in all measures for the 15 mg/day group starting by week one and for the 5 and 10 mg/day group by week two.

A placebo-controlled multicenter trial of aripiprazole (Werner et al., 2008) was completed in 296 patients aged 10-17 years with the diagnosis of bipolar I disorder, manic or mixed episode, with or without psychosis. The subjects were randomly assigned to receive aripiprazole 10 mg, 30 mg or placebo daily. On the Young Mania Rating Scale (YMRS) 50% of the 10 mg/day group were deemed responders (i.e.: more than 50% reduction in symptoms) while in the 30 mg/day group 56% of its subjects were responders. Both groups had significant reductions compared to placebo starting at week one.

Nine open-label prospective studies were found for aripiprazole in children and adolescents as well as several case reports, case series and retrospective chart reviews. The major diagnostic categories studied were Tourette Disorder, Aggression with varying underlying diagnosis, Bipolar Disorder and ADHD.

There were eight articles on the use of aripiprazole in tic disorders. Three were open label studies that looked at the use of aripiprazole in Tourette Disorder (Seo, Sung, Sea & Bai, 2008, Yoo, Kim & Kim, 2006 and Miranda & Castiglioni, 2007). Outcomes in all three studies were measured by the Yale Global Tic Severity Scale (YGTSS) at baseline and endpoint. In all three studies, significant reductions in the YGTSS were noted in participants aged 7-19 years with doses ranging between 2.5-20 mg/day. In two of the three studies CGI-I and CGI-S scales also showed significant reductions at endpoint. In addition to these open label studies there was a pilot study (Yoo et al., 2006), three case series (Murphy et al., 2005, Duane, 2006, Davies, Stern, Agrawal & Robertson, 2006) and one retrospective study (Budman et al., 2008) all finding clinical improvement with reasonable tolerability with use of aripiprazole in the treatment of tic disorders.

There were five articles on the use of aripiprazole in irritability and aggression. Two of the five studies were open-label trials looking at use of aripiprazole for irritability and aggression in either the PDD population or in patients with aggression regardless of underlying diagnosis. Stigler (Stigler et al., 2009) found significant improvement in 22 of 25 patients with PDD over a 14 week trial

with a dose range of 2.5-15 mg in patients aged 5-17 years. Outcomes were based on the CGI-I scale and the ABC-I. Bastiaens (Bastiaens, 2008) found clinical improvement on the Overt Aggression Scale (OAS) in 20 subjects, aged 6-17 years with severe aggression regardless of diagnosis in after two months of treatment with aripiprazole with a mean dose of 4.5 +/- 2.3 mg/day. In this same trial 14 subjects completed a trial of ziprasidone 42.9 +/- 18 mg/day with no significant differences noted between groups at baseline or after two months of treatment. There are also two retrospective reviews (Rugino & Janvier, 2005 and Valicenti-McDermott & Demb, 2006) and one case series (Stigler, Posey & McDougle, 2004) which looked at target symptoms of irritability and aggression in individuals with Pervasive Developmental Disorders (PDD), Development Disabilities (DD) or Bipolar Disorder diagnosis. Aripiprazole was found to be effective and tolerated, however an Autism Diagnosis comorbid with mental retardation (MR) predicted a worse outcome.

There were four articles in addition to the above mentioned RCTs on the use of aripiprazole in Bipolar Disorder or Bipolar Disorder Comorbid with Attention-Deficit/Hyperactivity Disorder (ADHD). Two of the four articles were open label studies. Biederman (Biederman et al., 2007) found a significant improvement of 30% reduction on the YMRS in 15 of 19 participants, aged 6-17 years on aripiprazole 9.4 mg/day monotherapy for 8 weeks. There was also a significant reduction in the Brief Psychiatric Rating Scale (BPRS) scores with the exception of the negative symptom profile and no improvement in symptoms of depression as measured by the Children's Depression Rating Scale (CDRS). Tramontina (Tramontina, Zeni, Pheula, de Souza & Rohde, 2007) treated ten children and adolescents aged 8-17 years with juvenile bipolar disorder comorbid with ADHD for 6 weeks. YMRS was used to assess severity of mania and the Swanson, Nolan and Pelham Scale-Version IV (SNAP-IV) was used to monitor ADHD. CGI-S was also utilized. Significant improvement was noted on all measures, including the SNAP-IV and most notably a 30% improvement on the YMRS in 70% of the subjects. Two retrospective case series (Barzman et al., 2004, Durkin, 2004) in Bipolar patients with or without comorbid ADHD supports the view that aripiprazole may be effective and well tolerated in this population.

One open label study (Findling et al., 2008b) enrolled youths aged 8-12 years with a diagnosis of ADHD into a 6 week trial. Outcome measures included the ADHD Rating Scale-IV (ARS-IV), CGI-I, CGAS, Conners' Continuous Performance Test II, Woodcock-Johnson subscales and the Stroop Color and Word Test. Fourteen youth were given

a mean aripiprazole dose of 6.7 mg/day which led to overall significant improvement from baseline on ARS-IV (both inattentive and hyperactive symptoms) and functional outcome (CGI-I). There were no improvements or deterioration noted on cognitive measures.

Woods (Woods et al., 2007) enrolled 15 participants with a mean age of 17.1 years meeting criteria for prodromal psychosis as identified by the Criteria of Prodromal Syndromes (COPS) in conjunction with the Structured Interview for Prodromal Syndromes (SIPS). Scale of Prodromal Symptoms (SOPS) was used to measure outcome and found significant reduction from baseline at eight weeks. Aripiprazole dose range was 5-30 mg/day in addition to the pre-enrollment prescribed antidepressant, mood stabilizer or stimulant. Thirteen subjects completed treatment with no subjects converting to psychosis over an 8 week period.

### Safety Data

Atypical antipsychotics as a group are generally associated with a lower risk of extrapyramidal symptoms (EPS) as identified by tremor, dystonia, akathisia, cogwheel rigidity than typical antipsychotics but generally have significant weight gain, hyperglycemia and dyslipidemia as their adverse effects. Risperidone is associated with hyperprolactinemia and ziprasidone is associated with QTc interval prolongation on the electrocardiogram (EKG). The main side effects reported in the previously mentioned articles were sedation/somnolence in as high as 50-78% of subjects in some studies. This resolved somewhat with lower doses, slower dosage titration and time. The development of EPS and akathisia was notable in most studies (incidence range: 8-28%) although usually in the mild – moderate range of severity. One individual receiving fixed-dose aripiprazole 25 mg/day dropped out of a study due to dystonia (Findling et al., 2008c) and in one study, medications were used to treat akathisia. Though potentially problematic, and in the absence of comparative studies with other antipsychotics, these reactions do not appear to occur as frequently or with the same degree of severity as with high-potency first generation antipsychotic agents. There is uncertainty at this time regarding the potential for development of Tardive Dyskinesia (TD) with use of aripiprazole in the child and adolescent population. The adult literature shows both development of TD as well as resolution of TD with aripiprazole treatment. There are 4 case reports of potential Neuroleptic Malignant Syndrome (NMS) with aripiprazole. One patient was treated with dantrolene (Palakurthi, Parvin & Kaplan, 2007), two patients were treated with lorazepam (Hamerman, Lam & Caroff, 2006, Groff & Coffey, 2008) and one continued with aripiprazole therapy

with resolution of symptoms (Strawn & Delgado, 2007).

Nausea, vomiting and gastrointestinal upset as well as headache symptoms were found to be common ( $\geq 10\%$ ) which almost always resolved with time and could be avoided through slower titration (Findling et al., 2004, Findling, 2008d.)

Treatment with aripiprazole in all 4 RCTs (Findling et al., 2008a, Owen et al., 2008a, Owen et al., 2008b, Werner et al., 2008) did not result in significant increases in weight or Body Mass Index (BMI) even following a 26-week continuation phase in one RCT (Werner et al., 2008). In one open-label study, weight gain appeared to be associated with higher aripiprazole dosage and longer duration of treatment (Stigler et al., 2009). In a contrasting study, some patients lost significant amounts of weight when switched to aripiprazole from an alternate atypical antipsychotic. (Stigler et al., 2004) In the few studies (Biederman et al., 2007, Findling et al., 2008a, 2008b, Owen et al., 2008a, 2008b, Stigler et al., 2009, Werner et al., 2008) that specifically looked at metabolic parameters (cholesterol, fasting glucose, triglycerides), there were no significant changes identified. There is one case report (Logue, Gonzalez, Heligman, McLaughlin & Belcher, 2007) of severe hyperglycemia and one case report (Dhamija & Verma, 2008) of diabetic ketoacidosis in young children receiving aripiprazole.

Aripiprazole has no warnings pertaining to cardiac functioning (Bristol-Myers Squibb Canada, 2009) and may even decrease QTc interval (Goodnick, Jerry & Parra, 2002). Studies that evaluated prolactin levels (Findling et al., 2008b, Stigler et al., 2009, Werner et al., 2008) found that aripiprazole may reduce prolactin rather than causing hyperprolactinemia. One case report (Wahl & Ostroff, 2005) found addition of aripiprazole effective in reducing symptomatic hyperprolactinemia in a patient on an alternate antipsychotic medication.

Melhem (Melhem, Katz, Jameson, Shellenbarger & Akhtar, 2009) summarized 10 cases of overdose in which children presented with profound somnolence, ataxia, nausea and vomiting as well as EPS with varying doses. Overdose in adolescents with acute or chronic dosing was tolerated well with minor lethargy only. Children under the age of 5 years were particularly susceptible to prolonged neurological manifestations from relatively small ingestions. EKG findings from these cases support that aripiprazole has no impact on cardiac conduction.

### Discussion and Recommendations

As is typical when reviewing pharmacotherapy evidence for this age group, there are very few RCTs with aripiprazole and given this consideration it should be considered as a second-line treatment option for limited indi-

cations. This medication is relatively new even in the adult population, and without the experience of time and the relative lack of excellent efficacy and safety data there is not enough evidence to support its use as a first-line medication in the child and adolescent population. The place in therapy of aripiprazole for this age group should be re-evaluated as new clinical trial data becomes available.

As always, in any child or adolescent in distress regardless of diagnosis, all other factors need to be part of the decision making regarding prescription of antipsychotics. Particularly in the prepubertal child and the individual with Autism with or without MR a thorough review of medical conditions, family dynamics and the community networks need to be undertaken. These factors should also be considered even when faced with a clear diagnosis of a mood and/or psychotic disorder.

With aripiprazole becoming available, the question is whether it should be used routinely in the pediatric population. From the available evidence, use of aripiprazole could be justified in Bipolar Disorder (manic or mixed episodes) and Schizophrenia, both of which are FDA approved indications in the child and adolescent population. We are not aware of any head-to-head studies directly comparing aripiprazole to other antipsychotic agents in this age group, and therefore cannot comment on comparative efficacy of aripiprazole to other antipsychotic agents. Aripiprazole appears to have efficacy in the treatment of Tourette disorder and tic disorders and further evidence via RCT would be most welcome. There is also some evidence showing efficacy for aggression and irritability regardless of underlying diagnosis. It is difficult to interpret these trials as the underlying diagnosis ranged from conduct disorder to Autism with or without MR. The difficulty is determining whether the decrease in aggression and irritability is due to treatment of the underlying disorder or due to sedation which could conceivably cause a paradoxical reaction in the population with comorbid Autism and MR.

There appear to be some potential advantages with use of aripiprazole. One is that EKG monitoring is not required as it has not been shown to have an impact on cardiac conduction even in overdose. A second advantage is the long half-life which facilitates once daily dosing. A significant incidence of sedation and somnolence secondary to aripiprazole therapy was noted in most trials. Although none of the trials specifically assessed changes in sleep parameters or use of concurrent hypnotic medications, it may be logical to administer this medication at bedtime to take advantage of its sedating effects. Another possible advantage is that aripiprazole can be used when individuals are particularly susceptible to

hyperprolactinemia induced by other agents. Finally, the impact of aripiprazole treatment on metabolic parameters such as weight, fasting glucose and lipids does appear to be less than some of the other available atypical agents when used in children and adolescents.

With regard to aripiprazole dosing in children and adolescents, higher doses (30 mg/day) compared to lower doses (10 mg/day) had a greater side effect burden without clearly superior efficacy in the Schizophrenia and Bipolar RCTs (Findling et al., 2008a, Werner et al., 2008). Given that side effects appear to be reduced through slower upwards dosage titration, our recommendation is to follow the US Prescribing Information (Otsuka Pharmaceutical Co., 2008) for aripiprazole in children and adolescents. Their recommendation is a starting daily dose of 2 mg titrated to 5 mg/day after 2 days and then to the target dose of 10 mg/day after 2 additional days. Clinical evaluation will guide the clinician regarding increasing the dose past 10 mg/day. If this is done, further dose increases should occur in 5 mg increments.

With regards to dosing aripiprazole in Tourette and tic disorders and/or ADHD, there are no clear guidelines. Aripiprazole doses for treatment of these indications ranged from 6.7 to 14.5 mg/day in the available reports (Budman et al., 2008, Davies et al., 2006, Findling et al, 2008b, Miranda & Castiglioni, 2008, Murphy et al., 2005, Seo et al., 2008, Yoo et al., 2006, Yoo et al., 2007). A dose of 10 mg/day appears to be a reasonable target dose for these conditions for most children and adolescents. Given that younger children are more susceptible to the side effects of aripiprazole (EPS, nausea and vomiting and sedation/somnolence) they should be started at lower initial doses with a lower target dose. The same can be said for use of aripiprazole for treatment of irritability and aggression particularly in the population with PDD and/or MR.

Aripiprazole will be available in Canada in 2, 5, 10, 15, 20 and 30 mg tablets. Unfortunately, it will not be made available in formulations that may help promote medication administration in children who have difficulty swallowing oral tablets, such as an oral liquid or oral disintegrating tablets (ODT), both of which are available in the US. A short-acting formulation for intramuscular injection is also marketed in the US, but will not be available in Canada.

Since a number of patients taking aripiprazole developed EPS including dystonia, akathisia, tremor and cog-wheel rigidity, it is our recommendation that patients be informed of the possibility of, and assessed routinely for these adverse effects. Dosage reduction of aripiprazole or introduction of either an anticholinergic agent or benzodiazepine may be required especially if clinical response

warrants ongoing use of aripiprazole. There is uncertainty regarding the relationship between aripiprazole and tardive dyskinesia so it is warranted and prudent to perform Abnormal Involuntary Movements Scale (AIMS) testing at baseline and periodically.

Despite evidence that aripiprazole is weight neutral and has minimal and insignificant impact on metabolic parameters in short term studies, our recommendation is to follow the 2004 Guidelines of the Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes (Barrett et al., 2004) for baseline and follow-up monitoring of metabolic parameters.

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The authors have no financial relationships to disclose.

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